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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,168	WEST ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9 and 24-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9 and 24-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/29/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/05 has been entered.

2. Claims 1-5, 7-9 and 24-35 are pending and are being acted upon in this Office Action.

3. The internal search reports on PTO 1449, filed 6/15/05 have been considered but crossed out because it is not appropriate to be print on an issued patent.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for making a tissue engineering scaffold as set forth in claims 1-5, 8 and 9, **does not** reasonably provide enablement for a method for making a tissue engineering scaffold using any matrix-enhancing molecule, any matrix-enhancing molecule such as TGF beta, angiotensin II, insulin like growth factor and ascorbic acid at any concentration sufficient to elicit production of any extracellular matrix by any cell, any cell such as smooth muscle cells, endothelial cells, fibroblasts, chondrocytes, and any combination thereof attached to any engineering scaffold without increasing cellular proliferation of the attached cells as set forth in claims 24-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection

are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only TGFbeta at optimal concentration in the range of between one and five ng TGF-β/ml, which is equivalent to between 4 x 10^{-6} and 4x 10^{-3} nmol/ml covalently coupled to hydrogel via polyethylene glycol for inducing extracellular matrix production by aortic smooth muscle cells.

The specification does not teach how to make all "matrix-enhancing molecule" for the claimed method without the amino acid sequence. Given the unlimited number of matrix enhancing molecules, there is insufficient guidance as to which matrix enhancing molecules would induce the production of which extracellular matrix by which cell type without increasing cellular proliferation of the attached cells to the scafold, much less at which particular concentration for the claimed method. Further, there is insufficient working example showing that any matrix enhancing molecule is effective for inducing matrix production in all cell type, in turn, would be useful for implantation. The specification does not teach how to predict which matrix-enhancing molecule is effective for inducing matrix production by which cell type.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Given the unlimited number of matrix enhancing molecules and without the structure (i.e. chemical structure of amino acid sequence), it is unpredictable which undisclosed matrix-enhancing molecule at which concentration is effective for inducing which matrix production for the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the

specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

6. Claims 24-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any matrix-enhancing molecule, any matrix-enhancing molecule such as TGF beta, angiotensin II, insulin like growth factor and ascorbic at any concentration sufficient to elicit production of (2) any extracellular matrix by (3) any cell attached to any engineering scaffold.

The specification discloses only TGFbeta at optimal concentration in the range of between one and five ng TGF-β/ml, which is equivalent to between 4 x 10^{-6} and 4x 10^{-3} nmol/ml covalently coupled to hydrogel via polyethylene glycol for inducing extracellular matrix production by aortic smooth muscle cells.

With the exception of the specific matrix-enhancing molecule to eliciting matrix production in only smooth muscle cells for the claimed method, there is insufficient written description about the structure associated with function of all matrix-enhancing molecule to induce matrix production in any other cells for the claimed method. Given the unlimited number of matrix-enhancing molecule, the concentration effective for each undisclosed matrix-enhancing molecule for which cell type for the claimed method is not adequately described.

The specification discloses only a method of making tissue engineering scaffold using only TGFbeta covalently coupled to PEG-diacrylate hydrogel, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of matrix-enhancing molecule to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 24, 28, 31 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat 5,162,430 (Nov 10, 1992; PTO 892).

The '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular). The reference polyethylene glycol has a molecular weight of between 1900, and about 8,000, which is between the claimed 200 and 10,000 (see col. 5, line 39, in particular). The reference tissue engineering is useful for tissue or organ implantation or tissue regeneration (see col. 4, line 28-40, in particular). Thus, the reference teachings anticipate the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-2, 4, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular). The reference polyethylene glycol has a molecular weight of between 1900, and about 8,000, which is between the claimed 200 and 10,000 (see col. 5, line 39, in particular). The reference tissue engineering is useful for tissue or organ implantation or tissue regeneration (see col. 4, line 28-40, in particular).

The claimed invention in claim 1 differs from the reference only in that the method wherein the TGF-beta is present at a density of between 1 and 100 ng/ml or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to

five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use TGFbeta a concentration 1-10 ng/ml as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells where the TGF is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent and Dinbergs *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

12. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs et al (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892) as applied to claims 1-2, 4, 8 and 9 and further in view of Scott-Burden et al (J Cardiovasc Pharmacol 16 Suppl 4: S36-41, 1990; PTO 892).

The combined teachings of the '430 patent and Dinbergs et al have been discussed supra.

The claimed invention in claim 3 differs from the teachings of the references only in that the method wherein the matrix-enhancing molecule is angiotensin II.

Scott-Burden et al teach angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TGF beta as taught by the '430 patent and Dinbergs et al for the angiotensin II as taught by Scott-Burden et al for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell where the angiotensin II is covalently coupled to collagen via a polymer tethered such as PEG as taught by the '430 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells as well as the growth of smooth muscle cell as taught by Scott-Burden et al (see abstract, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

13. Claims 5, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892) as applied to claims 1-2, 4, 8 and 9 and further in view of US Pat No. 5,935,849 (Aug 10, 1999; PTO 892).

The combined teachings of the '430 patent and Dinbergs et al have been discussed supra.

The claimed invention in claim 5 differs from the teachings of the references only in that the method wherein the matrix-enhancing molecule is ascorbic acid.

The claimed invention in claim 7 differs from the teachings of the references only in that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 8 differs from the references only in that the method wherein the scaffold hydrogel is alginate and combination thereof.

The '849 patent teaches a method of making a tissue engineering scaffold such as bioartificial organ (BAO) using scaffold such as hydrogel or alginate or collagen (see col. 19, lines 22, col. 20, lines 42-36, summary of invention, in particular) covalently

coupling to an inner matrix by a tether such as poly-d-lysine (see col. 18, line 30-35, in particular) coupling to matrix enhancing molecule such as RGD containing sequence (see col. 18, lines 36-51, in particular) or TGF beta and/or ascorbic acid (see col. 12, line 56-67, in particular). The '849 patent teaches TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells while ascorbic acid and TGFbeta1 increase collagen biosynthesis (see col. 12, lines 57-67, Table 1, in particular). The reference method further comprises providing cells such as fibroblast or endothelial cells attached within the tissue-engineering scaffold (see col. 16, Table 1, Col. 19, line 29, in particular). The reference method is useful for implantation and controlling distribution of cells within the bioartificial organ (see claims of '849 patent).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the hydrogel such as alginate and ascorbic acid as taught by the '849 patent for a method of making a tissue engineering scaffold comprising the hydrogel such as alginate covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix-enhancing molecule such as TGFbeta and/or ascorbic acid as taught by the '430 patent, Dinbergs et al and the '849 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells, while ascorbic acid and TGFbeta1 increase collagen biosynthesis as taught by the '849 patent (see col. 12, lines 57-67, Table 1, in particular). The use of engineering scaffold is useful to control cell number, cell distribution and attachment in organ transplant as taught by the '849 patent. Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

14. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892) as applied to claims 1-2, 4, 8 and 9 and further in view of WO 94/23740 (of record, Oct 1994, PTO 1449) or WO 96/27657 (Sept 1996; PTO 1449).

The combined teachings of the '430 patent and Dinbergs et al have been discussed supra.

The claimed invention in claim 8 differs from the teachings of the references only in that the method wherein the scaffold is a hyaluronic acid or polyethylene glycol polymer instead of collagen.

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently coupling to polyethylene glycol (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) covalently coupled to a scaffold such as hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or alginate, (See page 17, line 8, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the polyethylene glycol as taught by the WO 94/23740 publication or the hyaluronic acid as taught by the WO 96/27657 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in

the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because polyethylene glycol covalently to TGFβ2 is useful for stimulation of bone formation at a lower dose as taught by the WO 94/23740 publication (See abstract, in particular). The WO 96/27657 publication teaches hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or alginate coupled to TGFβ is useful for localized the desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

15. Claims 24-27 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of US Pat No. 5,935,849 (Aug 10, 1999; PTO 892).

The teachings of the '430 patent have been discussed supra.

The claimed invention in claim 25 differs from the reference only in that the method further comprises providing cell attached to the tissue engineering scaffold.

The claimed invention in claim 26 differs from the reference only in that the method further comprises providing cell attached to the tissue engineering scaffold wherein the cell is attached within the scaffold.

The claimed invention in claim 27 differs from the reference only in that the method wherein the cell is selected from the group consisting of endothelial cells, fibroblasts, and combination thereof.

The claimed invention in claim 32 differs from the reference only in that the method wherein the matrix enhancing molecule is ascorbic acid.

The claimed invention in claim 33 differs from the reference only in that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 33 differs from the reference only in that the method wherein the scaffold hydrogel is alginate, hyaluronic acid, polyethylene glycol· polymers and combination thereof.

The '849 patent teaches a method of making a tissue engineering scaffold such as bioartificial organ (BAO) using scaffold such as hydrogel or alginate or collagen (see col. 19, lines 22, col. 20, lines 42-36, summary of invention, in particular) covalently coupling to an inner matrix by a tether such as poly-d-lysine (see col. 18, line 30-35, in

particular) coupling to matrix enhancing molecule such as RGD containing sequence (see col. 18, lines 36-51, in particular) or TGF beta and/or ascorbic acid (see col. 12, line 56-67, in particular). The '849 patent teaches TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells while ascorbic acid and TGFbeta1 increase collagen biosynthesis (see col. 12, lines 57-67, Table 1, in particular). The reference method further comprises providing cells such as fibroblast or endothelial cells attached within the tissue engineering scaffold (see col. 16, Table 1, Col. 19, line 29, in particular). The reference method is useful for implantation and controlling distribution of cells within the bioartificial organ (see claims of '849 patent).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute (1) the collagen taught by the '430 patent for the hydrogel such as alginate as taught by the '849 patent and (2) the TGFbeta taught by the '430 patent for the TGFbeta and/or ascorbic acid as taught by the '849 patent for a method of making a tissue engineering scaffold comprising the hydrogel such as alginate covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix-enhancing molecule TGFbeta and/or ascorbic acid as taught by the '430 patent and the '849 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells, while ascorbic acid and TGFbeta1 increase collagen biosynthesis as taught by the '849 patent (see col. 12, lines 57-67, Table 1, in particular). The use of engineering scaffold is useful for controlling the cell number, the cell distribution and attachment in organ transplant as taught by the '849 patent. The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

16. Claims 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of 5,935,849 (Aug 10, 1999; PTO 892) as applied to claims 24-27 and 32-34 mentioned above and further in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The combined teachings of the '430 patent and the '849 patent have been discussed supra.

The claimed invention in claim 27 differs from the references only in that the method wherein the cell is smooth muscle cells.

The claimed invention in claim 29 differs from the references only in that the method wherein the TGF-beta is present at a density of between 1 and 100 ng/ml or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute fibroblast as taught by the '849 patent for the smooth muscle cell or endothelial cells and matrix enhancing molecule TGFbeta at concentration 1-10 ng/ml as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells where the TGF is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent, the '849 patent and Dinbergs *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular) and that TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The use of engineering scaffold is useful for controlling the cell number, the cell distribution and attachment in organ transplant as taught by the '849 patent. The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

17. Claims 24 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Scott-Burden et al (J Cardiovasc Pharmacol 16 Suppl 4: S36-41, 1990; PTO 892).

The teachings of the '430 patent have been discussed supra.

The claimed invention in claim 30 differs from the reference only in that the method wherein the matrix-enhancing molecule is angiotensin II instead of TGF beta.

Scott-Burden et al teach angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute TGFbeta as taught by the '430 patent for the angiogensin II as taught by Scott-Burden et al for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell where the angiotensin II is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent, the '849 patent and Scott-Burden et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because angiogensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell as taught by

Scott-Burden et al (see abstract, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

18. Claims 24 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of WO 94/23740 (of record, Oct 1994, PTO 1449) or WO 96/27657 (Sept 1996; PTO 1449).

The teachings of the '430 patent have been discussed supra.

The claimed invention in claim 34 differs from the reference only in that the method wherein the scaffold is hyaluronic acid or polyethylene glycol polymers.

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently coupling to polyethylene glycol (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) covalently coupled to a scaffold such as hyaluronic acid (see page 7, line 1, in particular) or collagen, or polyethylene oxide, or alginate, (See page 17, line 8, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the polyethylene glycol as taught by the WO 94/23740 publication or the hyaluronic acid or polyethylene oxide, or alginate as taught by the WO 96/27657 publication. From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because polyethylene glycol covalently to TGFβ2 is useful for stimulation of bone formation at a lower dose as taught by the WO 94/23740 publication (See abstract, in particular). The WO 96/27657 publication teaches hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or alginate coupled to TGFβ is useful for localized the desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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